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LOW EXPRESSION OF T-CELL RECEPTOR-CD3 COMPLEX: A CASE WITH A CLINICAL PRESENTATION RESEMBLING HUMORAL IMMUNODEFICIENCY*

*Özden Sanal MD***, *Leman Yel MD****, *Fügen Ersoy MD***
*İlhan Tezcan MD*****, *A. İzzet Berkel MD***

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Low expression of T-cell receptor-CD3 (TCR-CD3) complex, a rare cause of combined immunodeficiency, has only recently begun to be recognized. Here we report a four-year-old boy who has defective TCR-CD3 complex expression presenting with recurrent chest infections and pulmonary symptoms implying bronchial asthma. In our opinion, this entity should be borne in mind as the possible underlying defect in children with combined immunodeficiency having signs and symptoms of humoral immunodeficiency.
Key words: severe combined immunodeficiency, T-cell receptor, CD3 complex.

Combined immunodeficiencies are a group of diseases characterized clinically and immunologically by defects in both T and B lymphocytes. The clinical presentation usually includes failure to thrive and unusually persistent and potentially lethal infections with low virulence opportunistic organisms in infancy. However, the underlying T-cell defect is heterogeneous, leading to a wide spectrum of symptomatology[1-6]. Low expression of T-cell receptor-CD3 (TCR-CD3) complex, a rare cause of combined immunodeficiency, has only recently begun to be recognized and has been described in only three children, of whom two had clinical problems[2,4].

Here, we report a four-year-old male patient who had defective expression of the TCR-CD3 complex, presenting with recurrent chest infections and pulmonary symptoms implying bronchial asthma.

Case Report

A four-year-old boy was referred to the Immunology Unit, Hacettepe University Children's Hospital, because of recurrent pulmonary infections. He has born after and uncomplicated term pregnancy with a body weight of 3000 g as the eighth

* From the Immunology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

*** Pediatrician, Hacettepe University Faculty of Medicine.

**** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.

child of first-degree consanguineous parents. Frequent cough and wheezing usually with fever had been the major complaints since the age of six months. Chest infections had been diagnosed and treated with various antibiotics on more than 10 occasions, twice requiring hospitalization. Two months before he was referred, bronchial asthma was diagnosed and he was put on ketotifen and cromolyn sodium, resulting in amelioration. In addition to pulmonary symptoms, he had experienced urinary tract infections. BCG (Bacille Calmette Guerin), DPT-OPV (Diphteria, pertussis, tetanus, oral polio vaccine), and measles vaccinations had been administered without any complications. The developmental stages were within normal limits. He had recovered from chicken pox spontaneously at two years of age. Three of his siblings had died: the first sibling (female) of chicken pox at the age of 18 months, the third sibling (female) of measles at the age of 15 months, and the fourth (female) probably of leukemia (according to the history given by the family) at the age of 11 months. The remaining one male and three female siblings were healthy. There was no history of frequent infections in the family.

On physical examination, the patient weighed 14 kg (10^{th} - 25^{th} percentile) and measured 96 cm (10^{th} - 25^{th} percentile). He had a refraction error of the eyes. The rest of the systemic findings were unremarkable with neither dysmorphic features nor bony abnormalities.

Table I: Laboratory Data of the Patient[1]

Hemoglobin		12 g/dl
White blood cell count		6100/mm3
Absolute neutrophil count		3782/mm3
Absolute lymphocyte count		2108/mm3 (2900-5100)
Serum IgG		10.6 g/L (7.45-18.04 g/L)
Serum IgM		0.76 g/L (0.52-2.97 g/L)
Serum IgA		0.42 g/L (0.44-2.44 g/L)
Isohemagglutinin (anti-B) (Blood group A Rh+)		1/64
Antibody to poliovirus (1)		1/28
(2)		1/256
(3)		1/16
Anti-microsomal antibody		1/100
Anti-thyroglobulin antibody		1/160
C3		59.5 mg/dl
C4		30.6 mg/dl
CH50		31 IU/ml
Delayed type hypersensitivity	(PHA)	(+)*
	(Candida)	(+)
	(ppd)	(+)
Lymphocyte subpopulations	(CD3)**	30% (62-69)
	(CD4)	22% (30-40)
	(CD8)	19% (25-32)
	(CD19)	25% (21-28)
In vitro lymphocyte transformation to***		
	(PHA)	755 cpm (control 94, 842 cpm)
	(Con A)	556 cpm (control 36, 794 cpm)
	(medium)	350 cpm (control 872 cpm)

Numbers in parentheses indicate age-related normal values.
PHA : Phytohemagglutinin.
Con : Concanavalin-A
ppd : Purified protein derivates.

* Induration of 4-5 mm.
** Fluorescence intensity was about 1/3 of normal (histogram obained by FACS analysis and with Leu-4 mAb).
*** Lymphocyte transformation to antigens could not be studied.

Some of the laboratory investigations are shown on Table I. T lymphocytes expressed CD3 at about one-third of normal fluorescence intensity. HLA typing was as follows: A2, A36, B27, B50, CW6, DR7, DR11, DQ2, DQ7.

Erythrocyte adenosine deaminase (ADA) activity was within normal limits (43.7 µmol uric acid/h/g Hb). The total eosinophil count was 200/mm^3, and bacteria and polymorphonuclear leukocytes were seen on the nasal smear. The chloride concentration in sweat was 10 mEq/L. X-ray disclosed chronic changes in the lung fields and maxillary sinusitis.

He was diagnosed as having combined immunodeficiency, and low expression of TCR-CD3 complex was suspected based on the slight lymphopenia, the diminished number and low fluorescence intensity of CD3$^+$ T lymphocytes, and the markedly defective in vitro lymphocyte transformation to mitogens. The diagnosis was kindly confirmed by further investigations performed by Dr. J. Vossen and Dr. M. van Tol, Department of Pediatrics, and Dr. F. Koning, Department of Immunohematology and Bloodbank, Leiden University Hospital, The Netherlands. Molecular studies of the patient and the family are currently in progress. Preliminary data strongly suggest the absence of CD3-γ chain protein.

Having been on intravenous immunoglobulin replacement therapy (400 mg/kg/month), the patient was well after eight months of follow-up at the outpatient clinic without having experienced recurrent infections.

Discussion

Combined immunodeficiencies are a group of heterogeneous, primary disorders with respect to clinical presentation as well as T and B lymphocyte functions[6]. In our patient who had laboratory findings consistent with T-cell immunodeficiency, adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency, and Major Histocompatibility Complex (MHC) class II deficiency were excluded by the relevant laboratory tests. The relatively mild clinical presentation, the pattern of T-cell subsets, and the low fluorescence intensity of CD3 on T lymphocytes were compatible with the diagnosis of low expression of TCR-CD3 complex, which was included in the combined immunodeficiencies by the report of a WHO Scientific Group in 1992[6].

The recognition of foreign antigens by T lymphocytes is a crucial step in a normal immune response. T lymphocytes recognize antigens by means of a group of membrane proteins called the TCR-CD3 complex. The T-cell receptor α and β heterodimer binds antigen, and the Cd3-γ, CD3-δ, CD3-ε, CD3-ζ and CD3-η chains function in signal transduction to the cell nucleus to trigger T-cell response. Helper (CD4+) T-cells are induced to secrete factors that help B lymphocytes synthesize specific antibodies, and cytotoxic (CD8+) T-cells are stimulated to

lyse virally infected cells[1]. Therefore, a defect in the expression of or function of the TCR-CD3 complex would be expected to cause a combined immunodeficiency. To date, reports of two families with this disorder from two different centers have been published. The proband in the Spanish family reported presented with failure to thrive at the age of eleven months, and thereafter chronic anorexia, diarrhea and recurrent bronchopneumonia developed. The patient died because of viral pneumonia and severe autoimmune hemolytic anemia at the age of three years[2,5]. His male sibling had a relatively benign clinical presentation with asthmatic bronchitis and allergic rhinitis and was healthy at the age of 10 years at the latest report[2,3]. In the family described by the French group, a four-year-old boy presented with recurrent pneumonia and otitis media at two years of age[4,7]. Low expression of the TCR-CD3 complex in this patient was due to an abnormal CD3-ε subunit[8], while the defect in the two siblings was in the CD3-γ chain protein[3]. The clinical presentation of our patient was particularly similar to the patient in the second family. Our patient had recovered from chickenpox spontaneously and did not experience life-threatening infections, while his two female siblings who probably had the identical immunologic defect had died of chickenpox and measles. The difference in clinical severity is proposed to be due to redundancy of the immune system, and the encounter with environmental insults was also observed in the Spanish siblings[2].

Finally, we believe that low expression of TCR-CD3 complex should be borne in mind as the possible underlying defect in children presenting with signs and symptoms of a humoral immunological deficiency.

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